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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,530	11/28/2000	Clay B. Siegall	9632-012	7001

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	7

DATE MAILED: 06/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/724,530	Siegall et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____ .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *26, 27, 32, 33, and 37-57* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *26, 27, 32, 33, and 37-57* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *6*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

2. Claims 38-57 have been added. Claims 26, 27, 32, 33 and 37-57 are pending and under consideration.

3. The amendment filed February 19, 2002 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: Claims 49 and 56 drawn to a human antibody. Applicant states that the specification supports this amendment and refers to page 24 lines 28-32 which state that the antibodies of the instant invention comprise humanized and chimeric antibodies.. This is insufficient to support claims drawn to human antibodies which differ from humanized antibodies in that they have human complementarity determining regions.

Applicant is required to cancel the new matter in the reply to this Office Action.

New Claim Rejections

4. Claims 49 and 56 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is made in reference to the new matter rejection above..

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. Claims 37, 41, 44, 45, 50 and 51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hirano et al (Blood, 1999, Vol. 93, pp. 2999-3007, reference CM of the IDS filed February 19, 2002) in view of Pound et al (International Journal of Immunology, 1998, Vol. 11, pp. 11-20, reference CL of the IDS filed February 19, 2002). Claims 37, 41, 44, 45 and 50 are drawn in part to a method for the treatment of cancer comprising the administration of a purified antibody which binds CD40, wherein said antibody increases the binding of CD40 ligand to CD40 receptor. Claim 51 embodies the method wherein CD40 ligand is also administered.

Hirano et al teach a method of inhibiting human breast carcinoma cells by soluble CD40 ligand. Hirano et al further teach that preliminary data indicates that ovarian carcinomas and bladder carcinomas are also inhibited in vitro by the CD40 ligand, suggesting that CD40 stimulation may be beneficial in a method of treatment of these tumors in vivo (page 3006, first column, lines 13-22). Hirano et al teach that the antiproliferative effects of the CD40 ligand is due to the induction of apoptosis and necrosis in cancer cells (page 3004, first column , last sentence of the paragraph headed "srhCD40L induces apoptosis in human breast carcinoma cells"). Hirano et al teach the concept of Activation Induced Cell Death (AICD) wherein signals which cause activation in normal cells result in growth-inhibition of transformed cells (page

3004, first column, first two sentences of the paragraph headed "srhCD40L induces apoptosis in human breast carcinoma cells"). Hirano et al suggest a composition comprising an anti-CD40 monoclonal antibody and the CD40 ligand, wherein the anti-CD40 antibody is not an antagonist of the CD40 receptor, in order to assess synergism between the CD40 ligand and the anti CD40 antibody (page 3006, first column, lines 6-12) as a possible method of treatment.

Pound et al teach the monoclonal antibody of 5C3 which increases the binding of the CD40 ligand to the CD40 receptor Thus, Pound et al teach that 5C3 is not an antagonist of the CD40 receptor as 5C3 antibody increases the binding of CD40 ligand to the CD40 receptor.

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to combine the 5C3 antibody with the CD40 ligand and administer said combination in a method of the treating breast, ovarian or bladder carcinomas. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Hirano suggesting the combination of CD40 ligand with an antibody which activates the CD40 receptor for the treatment of solid tumors such as breast, ovarian and bladder carcinomas, and the teachings of Pound et al on the 5C3 antibody which increases the binding of CD40 ligand to the CD40 receptor, thus providing a further activation signal which will induce AIDC according to the teachings of Hirano et al.

7. Claims 37, 41, 44-48, 50 and 51 rejected under 35 U.S.C. 103(a) as being unpatentable over Hirano et al and Pound et al as applied to claims 37, 41, 44, 45, 50 and 51 above, and further in view of deBoer et al (US 5,874,082). Claims 46, 47 and 48 specify that the administered antibody contains a human constant region, is a chimeric antibody and is a humanized antibody, respectively. Neither Hirano et al nor Pound et al teach a humanized 5C3 antibody.

DeBoer et al teach the humanized monoclonal antibodies of 5D12, 3A8 and 3C6 which bind to CD40 receptor and the efficacy of administering humanized anti-CD40 monoclonal antibodies versus murine antibodies in the treatment of human diseases (column 4, lines 14-19).

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to humanize the 5C3 antibody for administration to humans. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of deBoer et al on the desirability of avoiding HAMA responses during therapy and the improvements associated with the administration of humanized antibodies versus murine antibodies in the treatment of human diseases.

8. Claims 26, 27, 32, 33, 37-48, 50-55 and 57 rejected under 35 U.S.C. 103(a) as being unpatentable over Francisco et al (Journal of Biological Chemistry, 1997, Vol. 272, pp. 24165-24169) in view of Hirano et al (Blood, 1999, Vol. 93, pp. 2999-3007, reference CM of the IDS filed February 19, 2002) and Paulie et al (Journal of Immunology, 1989, Vol. 142, pp. 590-595) and deBoer et al (US 5,874,082).

The specification teaches that SEQ ID NO:8, 9 and 10 are the amino acid sequences of the CDRs of the S2C6 antibody, and that SEQ ID NO:2 and 7 are the variable regions of the S2C6 antibody. Thus the invention encompasses methods of treating cancer comprising the administration of proteins comprising the variable regions or the CDR regions of the S2C6 antibody fused to the human constant domain resulting in a humanized or chimeric antibody, and methods of treating cancer comprising the administration of proteins comprising the variable regions or the CDR regions of the S2C6 antibody fused to chemotherapeutic agents.

Francisco et al teach method of treating cancer by the administration of immunotoxins comprising the variable light chain region of the G28-5 antibody fused to the variable heavy chain region of the G28-5 antibody, wherein said single chain Fv was fused either to bryodin at the N-terminus (BD1-G28-5 sFv) or fused to the pseudomonas exotoxin at the carboxyl terminus (G28-5sFv-PE40). Francisco et al teach that these single chain immunotoxins were derived from the G28-5 antibody which binds the CD40 receptor. Francisco et al teach that lung, breast, colon and ovarian carcinomas were sensitive to G28-5sFv-PE40 (table 1), whereas B-lineage malignancies

were sensitive to both G28-5sFv-PE40 and BD1-G28-5 sFv. (Page 24168, first column, second paragraph and figure 5). Francisco et al do not teach fusion proteins comprising the CDRs or variable regions of the S2C6 antibody.

Paulie et al teach the S2C6 antibody binds the CD40 receptor at a proximal epitope to that bound by the G28-5 antibody (abstract). Paulie et al further teach that the S2C6 and the G28-5 antibodies showed very similar binding with respect to some 24 cell lines tested (page 592, second column last line to page 593, first column, line 4). Francisco et al teach that the G28-5 antibody binds to CD40 receptor on B-lineage malignancies. Thus it is reasonable to assume that the S2C6 antibody will bind to the CD40 receptor on B-lineage malignancies.

Hirano et al teach that while contacting breast carcinoma cells in vitro with anti-CD40 antibodies did not result in the inhibition of growth of said cells, administering anti-CD40 antibodies to SCID mice bearing transplanted breast carcinoma cells resulted in significant anti-tumor effects attributed to the induction of antibody-dependent cell-mediated cytotoxicity in vivo (page 3005, first column, line 5 to page 3006, first column, line 2). The antibody administered to the SCID mice was murine in origin, having a murine constant region. Hirano et al suggest a composition comprising an anti-CD40 monoclonal antibody and CD40 ligand, wherein the anti-CD40 antibody is not an antagonist of the CD40 receptor in order to assess synergism between the CD40 ligand and the anti CD40 antibody (page 3006, first column, lines 6-12).

DeBoer et al teach the humanized monoclonal antibodies of 5D12, 3A8 and 3C6 which bind to CD40 receptor and the efficacy of administering humanized anti-CD40 monoclonal antibodies versus murine antibodies in the treatment of human diseases (column 4, lines 14-19)

It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to substitute the variable heavy and light chains of the S2C6 antibody for the variable heavy and light chains of the G28-5 antibody in both the G28-5sFv-PE40 and BD1-G28-5 sFv constructs taught by Francisco et al. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Paulie et al

on the binding of the S2C6 and G28-5 antibodies to proximal epitopes on the CD 40 receptor, and the teachings of Francisco et al on the binding of the G28-5 antibody to the CD40 receptor on B-lineage malignancies.

It would have also been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to make a protein comprising the light and heavy variable chains of the S2C6 antibody fused to a human immunoglobulin constant domain and to use said protein in a composition with the CD40 ligand for a method of treating cancer. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Francisco et al and Paulie et al which render obvious a fusion protein comprising the light and heavy variable chains of the S2C6 antibody, for the reasons set forth above, and the teachings of Hirano et al on the anti-tumor effects of murine anti-CD40 antibodies against breast carcinoma cells in SCID mice, said anti-tumor affects attributed to ADCC; the suggestion of Hirano et al for a composition comprising an anti-CD40 monoclonal antibody and CD40 ligand, and the teachings of DeBoer et al, on the improvements afforded humanized anti-CD40 antibodies versus murine anti-CD40 antibodies.

9. All other rejections and objections as stated in Paper No. 4 are withdrawn in light of applicants arguments.

Conclusion

10. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on Fegruary 19, 2002 prompted the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

June 1, 2002

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